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Mendelian randomization study of the association between telomere length and risk of cancer and non-neoplastic diseases

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ABSTRACT 349 WORDS

Importance The causal direction and magnitude of the association between telomere length and incidence of cancer and non-neoplastic diseases is uncertain, due to the susceptibility of observational studies to confounding and reverse causation.

Objective To conduct a Mendelian randomization study, using germline genetic variants as instrumental variables, to appraise the causal relevance of telomere length for risk of cancer and non-neoplastic diseases.

Data Sources Genome-wide association studies (GWAS) published up to January 15 2015.

Study Selection GWAS of non-communicable diseases that assayed germline genetic variation and did not select cohort or control participants on the basis of pre-existing diseases. Of 163 GWAS of non-communicable diseases identified, summary data from 103 were available.

Data Extraction Summary association statistics for single nucleotide polymorphisms (SNPs) that are strongly associated with telomere length in the general population.

Main Outcomes Odds ratios (ORs) for disease per standard deviation (SD) higher telomere length due to germline genetic variation.

Results Summary data were available for 35 cancers and 48 non-neoplastic diseases, corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median 6,789 per disease). Increased telomere length due to germline genetic variation was generally associated with increased risk for site-specific cancers. The strongest associations were observed for (ORs per 1-SD change in genetically increased telomere length): glioma 5.27 (3.15-8.81), serous low-malignant-potential ovarian cancer 4.35 (2.39-7.94), lung adenocarcinoma 3.19 (2.40-4.22), neuroblastoma 2.98 (1.92-4.62), bladder cancer 2.19 (1.32-3.66), melanoma 1.87 (1.55-2.26), testicular cancer 1.76 (1.02-3.04), kidney cancer 1.55

(1.08-2.23) and endometrial cancer 1.31 (1.07-1.61). Associations were stronger for rarer cancers and at tissue sites with lower rates of stem cell division ($P<0.05$). There was generally little evidence of association between genetically increased telomere length and risk of psychiatric, autoimmune, inflammatory, diabetic and other non-neoplastic diseases, except for coronary heart disease (0.78 [0.67-0.90]), abdominal aortic aneurysm (0.63 [0.49-0.81]), celiac disease (0.42 [0.28-0.61]) and interstitial lung disease (0.09 [0.05- 0.15]).

Conclusions It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases.

INTRODUCTION

At the ends of chromosomes, telomeres are DNA-protein structures that protect the genome from damage, shorten progressively over time in most somatic tissues[1] and are proposed physiological markers of ageing.[2,3] Shorter leukocyte telomeres are correlated with older age, male sex and other known risk factors for non-communicable diseases[4–6] and are generally associated with higher risk for cardiovascular diseases[7,8], type 2 diabetes[9] and non-vascular non-neoplastic causes of mortality.[8] Whether these associations are causal, however, is unknown. Telomere length has also been implicated in risk of cancer but the direction and magnitude of the association is uncertain and contradictory across observational studies.[10–14] The uncertainty reflects the considerable difficulty of designing observational studies of telomere length and cancer incidence that are robust to reverse causation, confounding and measurement error.

The aim of the present report was to conduct a Mendelian randomization study, using germline genetic variants as instrumental variables for telomere length, to help clarify the nature of the association between telomere length and risk of cancer and non-neoplastic diseases. The approach, which mimics the random allocation of individuals to the placebo and intervention arms of a randomized controlled trial, allowed us to: (1) estimate the direction and broad magnitude of the association of telomere length with risk of multiple cancer and non-neoplastic diseases; (2) appraise the evidence for causality in the estimated etiological associations; (3) investigate potential sources of heterogeneity in findings for site-specific cancers; and (4) compare genetic estimates to findings based on directly measured telomere length in prospective observational studies.

METHODS

Study design

The design of our study, illustrated in Figure S1, had three key components: 1) the identification of genetic variants to serve as instruments for telomere length; 2) the acquisition of summary data for the genetic instruments from genome wide association studies (GWASs) of diseases and risk factors for non-communicable diseases; and 3) the classification of diseases and risk factors into primary or secondary outcomes based on *a priori* statistical power. As a first step, we searched the GWAS catalog[15,16] on the 15 January 2015, to identify single nucleotide polymorphisms (SNPs) associated with telomere length. To supplement the list with additional potential instruments, we also searched the original study reports curated by the GWAS catalog (using a P-value threshold of $5x10^{-8}$).[17–25] We acquired summary data for all SNPs identified by our search from a meta-analysis of GWASs of telomere length, involving 9,190 participants of European ancestry.[18]

The second key component of our design strategy involved the acquisition of summary data, corresponding to the selected genetic instruments for telomere length, from GWASs of non-communicable diseases and risk factors (Fig. S1). As part of this step, we invited principal investigators of non-communicable disease studies curated by the GWAS catalog[15,26] to share summary data for our study. We also downloaded summary data for diseases and risk factors from publically available sources, including study-specific websites, dbGAP, ImmunoBase and the GWAS catalog (Fig. S1).

The third key component of our design strategy was the classification of diseases and risk factors into either primary or secondary outcomes, which we defined on the basis of *a priori* statistical power to detect associations with telomere length. Primary outcomes were defined

as diseases with sufficient cases and controls for >50% statistical power and secondary outcomes defined as diseases with <50% statistical power to detect odds ratios ≥2.0 per standard deviation (SD) change in genetically increased telomere length (alpha assumed to be 0.01). All risk factors were defined as secondary outcomes. Risk factors with <50% statistical power were excluded.

Further details on our design strategy can be found in the supplement.

Comparison with prospective observational studies

We searched PubMed for prospective observational studies of the association between telomere length and disease (see Tables S3 and S4 for details of the search strategy and inclusion criteria). Study-specific relative risks for disease per unit change or quantile comparison of telomere length were transformed to a SD scale using previously described methods.[27] Hazard ratios, risk ratios and odds ratios were assumed to approximate the same measure of relative risk. Where multiple independent studies of the same disease were identified, these were combined by fixed effects meta-analysis, unless there was strong evidence of between-study heterogeneity ($P_{Cochran's\ Q}<0.001$), in which case they were kept separate.

Statistical analysis

We combined summary data across SNPs into a single instrument, using maximum likelihood to estimate the slope of the relationship between β_{GD} and β_{GP} and a variance-covariance matrix to make allowance for linkage disequilibrium between SNPs,[28] where β_{GD} is the change in disease log odds or risk factor levels per copy of the effect allele and β_{GP} is the SD change in telomere length per copy of the effect allele (see supplementary methods

144 for technical details). The slope from this approach can be interpreted as the log odds ratio for
145 binary outcomes, or the unit change for continuous risk factors, per SD change in genetically
146 increased telomere length. P-values for heterogeneity amongst SNPs, in the estimated
147 associations of genetically increased telomere length with disease and risk factors, were
148 estimated by likelihood ratio tests.[28] Associations between genetically increased telomere
149 length and continuous risk factors were transformed into SD units. For five secondary disease
150 outcomes where only a single SNP was available for analysis, we estimated associations
151 using the Wald ratio: $\beta_{GD}/\beta_{GP,}$ with standard errors approximated by the delta method.[29]

152 Inference of causality in the estimated etiological associations between telomere length and
153 disease depends on satisfaction of Mendelian randomization assumptions (Fig. S7; see Table
154 S6 for a glossary of terms).[30,31] The assumptions are: 1) the selected SNPs are associated with
155 telomere length; 2) the selected SNPs are not associated with confounders; and 3) the selected
156 SNPs are associated with disease exclusively through their effect on telomere length. If these
157 assumptions are satisfied, the selected SNPs are valid instrumental variables and their
158 association with disease can be interpreted as a causal effect of telomere length. We modeled
159 the impact of violations of these assumptions through two sets of sensitivity analyses: a
160 weighted median function[32] and MR-Egger regression[30] (see supplementary methods for
161 technical details). We restricted our sensitivity analyses to diseases showing the strongest
162 evidence of association with genetically increased telomere length (defined as
163 $P_{Bonferroni} \leq 0.05$).
164
165 We used meta-regression to appraise potential sources of heterogeneity in our findings for
166 cancer. The association of genetically increased telomere length with the log odds of cancer
167 was regressed on cancer incidence, survival time and median age-at-diagnosis, downloaded
168 from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)

Program,[33] and tissue-specific rates of stem cell division from Tomasetti and Vogelstein.[34] As the downloaded cancer characteristics from SEER correspond to the United States population, 77% of which was of white ancestry in 2015[35], the meta-regression analyses excluded genetic studies conducted in East Asian populations.

All analyses were performed in R version 3.1.2[36] and Stata release 13.1 (StataCorp, College Station, TX). P-values were two-sided and evidence of association was declared at $P<0.05$. Where indicated, Bonferroni corrections were used to make allowance for multiple testing, although this is likely to be overly conservative given the non-independence of many of the outcomes tested.

RESULTS

We selected 16 SNPs as instruments for telomere length (Fig. S1 & Table 1). The selected SNPs correspond to 10 independent genomic regions that collectively account for 2-3% of the variance in leukocyte telomere length, which is equivalent to an F statistic of ~18. This indicates that the genetic instrument, constructed from these 10 independent genomic regions, is strongly associated with telomere length (details in supplementary discussion).[37] Summary data for the genetic instruments were available for 83 non-communicable diseases, corresponding to 420,081 cases (median 2,526 per disease) and 1,093,105 controls (median 6,789 per disease), and 44 risk factors (Fig. S1, Table 2 and Table S1). The median number of SNPs available across diseases was 11 (min=1, max=13) and across risk factors was 12 (min=11, max=13). Of the 83 diseases, 56 were classified as primary outcomes and 27 as secondary outcomes (Table 2, Fig. S1 and Table S1). For 9 of the 83 non-communicable diseases, additional summary data were available from 10 independent studies for replication

194 analyses, corresponding to 40,465 cases (median 1,416 per disease) and 52,306 controls
195 (median 3,537 per disease) (Table S1).

196 The results from primary analyses of non-communicable diseases are presented in Figure 1;
197 results from secondary analyses of risk factors and diseases with low *a priori* power are
198 presented in the supplement (Fig. S2, S5 and S6). Genetically increased telomere length was
199 associated with higher odds of disease for 9 of 22 primary cancers ($P<0.05$), including (odds
200 ratio [95% confidence interval]): glioma (5.27 [3.15-8.81]), endometrial cancer (1.31 [1.07-
201 1.61]), kidney cancer (1.55 [1.08-2.23]), testicular germ cell cancer (1.76 [1.02-3.04]),
202 melanoma (1.87 [1.55-2.26]), bladder cancer (2.19 [1.32-3.66]), neuroblastoma (2.98 [1.92-
203 4.62]), lung adenocarcinoma (3.19 [2.40-4.22]) and serous low-malignancy-potential (LMP)
204 ovarian cancer (4.35 [2.39-7.94]) (Fig. 1). The associations were, however, highly variable
205 across cancer types, varying from an odds ratio of 0.86 (0.50-1.48) for head and neck cancer
206 to 5.27 (3.15-8.81) for glioma. Substantial variability was also observed within tissue sites.
207 For example, the odds ratio for lung adenocarcinoma was 3.19 (2.40-4.22) compared to 1.07
208 (0.82-1.39) for squamous cell lung cancer. For serous LMP ovarian cancer the odds ratio was
209 4.35 (2.39-7.94) compared to odds ratios of 1.21 (0.87-1.68) for endometrioid ovarian cancer,
210 1.12 (0.94-1.34) for serous invasive ovarian cancer, 1.04 (0.66-1.63) for clear cell ovarian
211 cancer and 1.04 (0.73-1.47) for mucinous ovarian cancer. The strongest evidence of
212 association was observed for glioma, lung adenocarcinoma, neuroblastoma and serous LMP
213 ovarian cancer ($P_{Bonferroni}<0.05$). Results for glioma and bladder cancer showed evidence for
214 replication in independent datasets (independent datasets were not available for other
215 cancers) (Fig. S3).

216 Genetically increased telomere length was associated with reduced odds of disease for 6 of 32
217 primary non-neoplastic diseases ($P<0.05$), including coronary heart disease (0.78 [0.67-0.9]),
218 abdominal aortic aneurysm (0.63 [0.49-0.81]), Alzheimer's disease (0.84 [0.71-0.98]), celiac

disease (0.42 [0.28-0.61]), interstitial lung disease (0.09 [0.05-0.15]) and type 1 diabetes (0.71 [0.51-0.98]) ($P<0.05$) (Figure 1). The strongest evidence of association was observed for coronary heart disease ($P_{Bonferroni}=0.05$) and abdominal aortic aneurysm, celiac disease and interstitial lung disease ($P_{Bonferroni}<0.05$). The associations with coronary heart disease and interstitial lung disease showed evidence for replication in independent datasets (Fig. S3).

Our genetic findings were generally similar in direction and magnitude to estimates based on observational prospective studies of leukocyte telomere length and disease (Figure 3). Our genetic estimates for lung adenocarcinoma, melanoma, kidney cancer and glioma, were, however, stronger in comparison to observational estimates.

In sensitivity analyses, we appraised the potential impact of confounding by pleiotropic pathways on our results. Associations estimated by the weighted median and MR-Egger were broadly similar to the main results for glioma, lung adenocarcinoma, serous LMP ovarian cancer, neuroblastoma, abdominal aortic aneurysm, coronary heart disease and interstitial lung disease (Fig. S4). In the second set of sensitivity analyses, implemented by MR-Egger regression, we found little evidence for the presence of pleiotropy ($P_{intercept}\geq0.27$) (Fig. S4). The MR-Egger analyses were, however, generally underpowered, as reflected by the wide confidence intervals in the estimated odds ratios.

In meta-regression analyses, we observed that genetically increased telomere length tended to be more strongly associated with rarer cancers ($P=0.02$) and cancers at tissue-sites with lower rates of stem cell division ($P=0.02$) (Figure 2). The associations showed little evidence of varying by percentage survival five years after diagnosis or median age-at-diagnosis ($P\geq37$).

DISCUSSION

In this report we show that genetically increased telomere length is associated with increased risk of several cancers and with reduced risk of some non-neoplastic diseases. Given the random distribution of genotypes in the general population with respect to lifestyle and other environmental factors, as well as the fixed nature of germline genotypes, these results should be less susceptible to confounding and reverse causation in comparison to observational studies. Our results could, however, reflect violations of Mendelian randomization assumptions, such as confounding by pleiotropy, population stratification or ancestry.[38] Although we cannot entirely rule out this possibility, the majority of our results persisted in sensitivity analyses that made allowance for violations of Mendelian randomization assumptions. Confounding by population stratification or ancestry is also unlikely, given the adjustments made for ancestry in the original disease GWASs (see supplementary discussion). Our results are therefore compatible with causality.

Comparison with previous studies

Our findings for cancer are generally contradictory to those based on retrospective studies, which tend to report increased risk for cancer in individuals with shorter telomeres.[11,12,39–42] The contradictory findings may reflect reverse causation in the retrospective studies, whereby shorter telomeres arise as a result of disease, or of confounding effects, e.g. due to cases being slightly older than controls even in age-matched analyses. Our findings for cancer are generally more consistent with those based on prospective observational studies, which tend to report weak or null associations of longer leukocyte telomeres with overall and site-specific risk of cancer,[10–13,41,43–62] with some exceptions.[63] Our results are also similar to previously reported Mendelian randomization studies of telomere length and risk of

melanoma, lung cancer, chronic lymphocytic leukemia and glioma.[64–67] The shape of the association with cancer may not, however, be linear over the entire telomere length distribution. For example, individuals with dyskeratosis congenita, a disease caused by germline loss-of-function mutations in the telomerase component genes *TERC* and *TERT,* have chronically short telomeres and are at increased risk of some cancers, particularly acute myeloid leukemia and squamous cell carcinomas arising at sites of leukoplakia,[68,69] presumably due to increased susceptibility to genome instability and chromosomal end-to-end fusions.[70] Our results should therefore be interpreted as reflecting the average association at the population level and may not be generalizable to the extreme ends of the telomere length distribution.

Mechanisms of association

Our cancer findings are compatible with known biology.[70] By limiting the proliferative potential of cells, telomere shortening may serve as a tumour suppressor; and individuals with longer telomeres may be more likely to acquire somatic mutations owing to increased proliferative potential.[70] Rates of cell division are, however, highly variable amongst tissues[34] and thus the relative gain in cell proliferative potential, conferred by having longer telomeres, may also be highly variable across tissues. This could explain the ~6-fold variation in odds ratios observed across cancer types in the present study, as well as the tendency of our results to be stronger at tissue sites with lower rates of stem cell division. For example, the association was strongest for glioma (OR=5.27) and comparatively weak for colorectal cancer (OR=1.09) and the rates of stem cell division in the tissues giving rise to these cancers differ by several orders of magnitude. In neural stem cells, which give rise to gliomas, the number of divisions is ~270 million and for colorectal stem cells is ~1.2 trillion over the average lifetime of an individual.[34] The observation that genetically increased telomere

length was more strongly associated with rarer cancers potentially reflects the same mechanism, since rarer cancers also tend to show lower rates of stem cell division.[34] For example, the incidence of glioma is 0.4 and for colorectal cancer is 42.4 per 100,000 per year in the United States.[33]

The inverse associations observed for some non-neoplastic diseases may reflect the impact of telomere shortening on tissue degeneration and an evolutionary trade-off for greater resistance to cancer at the cost of greater susceptibility to degenerative diseases, particularly cardiovascular diseases.[71,72]

Study limitations

Our study is subject to some limitations, in addition to the Mendelian randomization assumptions already considered above. First, our method assumes that the magnitude of the association between SNPs and telomere length is consistent across tissues. Second, our study assumed a linear shape of association between telomere length and disease risk, whereas the shape could be "J" or "U" shaped.[44,57,68] Third, our results assume that the samples used to define the genetic instrument for telomere length[18] and the various samples used to estimate the SNP-disease associations are representative of the same general population, practically defined as being of similar ethnicity, age and sex distribution.[73] This assumption would, for example, not apply in the case of the SNP-disease associations derived from East Asian or pediatric populations. Generally speaking, violation of the aforementioned assumptions could bias the magnitude of the association between genetically increased telomere length and disease; but would be unlikely to increase the likelihood of false positives (i.e. incorrectly inferring an association when none exists).[74] Our results should therefore remain informative for the direction and broad magnitude of the average association at the population level, even

in the presence of such violations. Fourth, we cannot rule out chance in explaining some of the weaker findings. Fifth, our results may not be fully representative of non-communicable diseases (since not all studies shared data and our analyses were underpowered for the secondary disease outcomes). The diseases represented in our primary analyses probably account for >60% of all causes of death in American adults.[75]

Clinical relevance of findings

Our findings suggest that potential clinical applications of telomere length, e.g. as a tool for risk prediction or as an intervention target for disease prevention, may have to consider a trade-off in risk between cancer and non-neoplastic diseases. For example, a number of companies have been established that offer telomere length measurement services to the public (via a requesting physician), under the claim that shorter telomeres are a general indicator of poorer health status and older biological age and that such information can be used to motivate healthy lifestyle choices in individuals. However, the conflicting direction of association between telomere length and risk of cancer and non-neoplastic diseases, indicated by our findings, suggests that such services to the general public may be premature.

Conclusion

It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. Further research is required to resolve whether telomere length is a useful predictor of risk that can help guide therapeutic interventions, to clarify the shape of any dose-response relationships and to characterise the nature of the association in population subgroups.

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399

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Table 1. Single nucleotide polymorphisms associated with telomere length

SNPs	Chr	Pos	Gene	EA	OA	EAF*	Beta*	SE*	P-value*	Phet*	No. studies*	Sample size*	Discovery p-value	% variance explained	Discovery study
rs11125529	2	54248729	*ACYP2*	A	C	0.16	0.065	0.012	0.000606	0.313	6	9177	8.00E-10	0.080	Codd[21]
rs6772228	3	58390292	*PXK*	T	A	0.87	0.041	0.014	0.049721	0.77	6	8630	3.91E-10	0.200	Pooley[17]
rs12696304	3	169763483	*TERC*	C	G	0.74	0.090	0.011	5.41E-08	0.651	6	9012	4.00E-14	0.319	Codd[22]
rs10936599	3	169774313	*TERC*	C	T	0.76	0.100	0.011	1.76E-09	0.087	6	9190	3.00E-31	0.319	Codd[21]
rs1317082	3	169779797	*TERC*	A	G	0.71	0.097	0.011	4.57E-09	0.029	6	9176	1.00E-08	0.319	Mangino[18]
rs10936601	3	169810661	*TERC*	C	T	0.74	0.087	0.011	8.64E-08	0.433	6	9150	4.00E-15	0.319	Pooley[17]
rs7675998	4	163086668	*NAF1*	G	A	0.80	0.048	0.012	0.008912	0.077	6	9161	4.35E-16	0.190	Codd[21]
rs2736100	5	1286401	*TERT*	C	A	0.52	0.085	0.013	2.14E-05	0.54	4	5756	4.38E-19	0.310	Codd[21]
rs9419958	10	103916188	*OBFC1*	T	C	0.13	0.129	0.013	5.26E-11	0.028	6	9190	9.00E-11	0.171	Mangino[18]
rs9420907	10	103916707	*OBFC1*	C	A	0.14	0.142	0.014	1.14E-11	0.181	6	9190	7.00E-11	0.171	Codd[21]
rs4387287	10	103918139	*OBFC1*	A	C	0.14	0.120	0.013	1.40E-09	0.044	6	8541	2.00E-11	0.171	Levy[25]
rs3027234	17	8232774	*CTC1*	C	T	0.83	0.103	0.012	2.75E-08	0.266	6	9108	2.00E-08	0.292	Mangino[18]
rs8105767	19	22032639	*ZNF208*	G	A	0.25	0.064	0.011	0.000169	0.412	6	9096	1.11E-09	0.090	Codd[21]
rs412658	19	22176638	*ZNF676*	T	C	0.35	0.086	0.010	1.83E-08	0.568	6	9156	1.00E-08	0.484	Mangino[18]
rs6028466	20	39500359	*DHX35*	A	G	0.17	0.058	0.013	0.003972	0.533	6	9190	2.57E-08†	0.041	Mangino[18] & Gu
rs755017	20	63790269	*ZBTB46*	G	A	0.17	0.019	0.0129	0.339611	0.757	5	8026	6.71E-09	0.090	Codd[21]

*Summary data from Mangino et al[18]; Chr, chromosome; pos, base-pair position (GRCh38.p3); EA, effect allele, OA, other allele, Beta, standard deviation change in telomere length per copy of the effect allele; SE, standard error; EAF - effect allele frequency; Phet - p value for between-study heterogeneity in association between SNP and telomere length; †from a meta-analysis of Mangino[18] and Gu[20] performed in the present study.

Table 2. Study characteristics for primary non-communicable diseases

	No. cases	No. controls	No. SNPs	Statistical power	Pop.	Study / First author
Cancer						
Bladder cancer	1601	1819	10	0.62	EUR	NBCS[76]
Breast cancer	48155	43612	13	1.00	EUR	BCAC[17,77]
Estrogen receptor –ve	7465	42175	13	1.00	EUR	BCAC[17,77]
Estrogen receptor +ve	27074	41749	13	1.00	EUR	BCAC[17,77]
Colorectal cancer	14537	16922	9	1.00	EUR	CORECT/GECCO[64,78]
Endometrial cancer	6608	37925	12	1.00	EUR	ECAC[79,80]
Esophageal SCC	1942	2111	11	0.64	EA	Abnet[81]
Glioma	1130	6300	12	0.72	EUR	Wrensch[82] & Walsh[66]
Head & neck cancer	2082	3477	12	1.00	EUR	McKay et al[83]
Kidney cancer	2461	5081	12	0.99	EUR	KIDRISK[84]
Lung cancer	11348	15861	13	1.00	EUR	ILCCO[85]
Adenocarcinoma	3442	14894	13	1.00	EUR	ILCCO[85]
Squamous cell carcinoma	3275	15038	13	1.00	EUR	ILCCO[85]
Skin cancer						
Melanoma	12814	23203	13	1.00	EUR	MC[86]
Basal cell carcinoma	3361	11518	13	1.00	EUR	NHS/HPFS[87]
Neuroblastoma	2101	4202	12	0.87	EUR	Diskin[88]
Ovarian cancer	15397	30816	13	1.00	EUR	OCAC[17,89]
Clear cell	1016	30816	13	0.76	EUR	OCAC[17,89]
Endometriod	2154	30816	13	0.98	EUR	OCAC[17,89]
Mucinous	1643	30816	13	0.94	EUR	OCAC[17,89]
Serous invasive	9608	30816	13	1.00	EUR	OCAC[17,89]
Serous LMP	972	30816	13	0.73	EUR	OCAC[17,89]
Pancreatic cancer	5105	8739	12	1.00	EUR	PanScan (incl. EPIC)[90]
Prostate cancer	22297	22323	11	1.00	EUR	PRACTICAL[91,92]
Testicular germ cell cancer	986	4946	11	0.52	EUR	Turnbull[93] & Rapley[94]
Autoimmune/inflammatory diseases						
Alopecia areata	2332	5233	7	0.60	EUR	Betz[95]
Atopic dermatitis	10788	30047	13	1.00	EUR	EAGLE[96]
Celiac disease	4533	10750	3	0.82	EUR	Dubois[97]
Inflammatory bowel disease						
Crohn's disease	5956	14927	11	1.00	EUR	IIBDGC[98]
Ulcerative colitis	6968	20464	12	1.00	EUR	IIBDGC[98]
Juvenile idiopathic arthritis	1866	14786	11	0.87	EUR	Thompson[99]†
Multiple sclerosis	14498	24091	3	1.00	EUR	IMSGC[100]
Aggressive periodontitis	888	6789	13	0.63	EUR	Schaefer[101]
Rheumatoid arthritis	5538	20163	11	1.00	EUR	Stahl[102]
Cardiovascular diseases						
Abdominal aortic aneurysm	4972	99858	13	1.00	EUR	AC[103–108]
Coronary heart disease	22233	64762	13	1.00	EUR	CARDIoGRAM[109]
Heart failure	2526	20926	13	0.99	EUR	CHARGE-HF[110]
Hemorrhagic stroke	2963	5503	12	0.96	EUR	METASTROKE/ISGC[111]
Ischemic stroke	12389	62004	13	1.00	EUR	METASTROKE/ISGC[112,113]
large vessel disease	2167	62004	13	0.99	EUR	METASTROKE/ISGC[112,113]
small vessel disease	1894	62004	13	0.97	EUR	METASTROKE/ISGC[112]
cardioembolic	2365	62004	13	0.99	EUR	METASTROKE/ISGC[112]
Sudden cardiac arrest	3954	21200	13	1.00	EUR	Unpublished
Diabetes						
Type 1 diabetes	7514	9045	6	0.95	EUR	T1DBase[114115]
Type 2 diabetes	10415	53655	11	1.00	EUR	DIAGRAM[116]
Eye disease						

AMD	7473	51177	13	1.00	EUR	AMD Gene[117]
Retinopathy	1122	18289	12	0.75	EUR	Jensen[118]
Lung diseases						
Asthma	13034	20638	4	1.00	EUR	Ferreira/GABRIEL[119,120]
COPD	2812	2534	12	0.85	EUR	COPDGene[121]
Interstitial lung disease	1616	4683	9	0.60	EUR	Fingerlin[122]
Neurological / psychiatric diseases						
ALS	6100	7125	12	1.00	EUR	SLAGEN/ALSGEN[123]
Alzheimer's disease	17008	37154	12	1.00	EUR	IGAP[124]
Anorexia nervosa	2907	14860	9	0.93	EUR	GCAN[125]
Autism	4949	5314	7	0.82	EUR	PGC[126]
Bipolar disorder	7481	9250	9	1.00	EUR	PGC[127]
Major depressive disorder	9240	9519	8	0.99	EUR	PGC[128]
Schizophrenia	35476	46839	12	1.00	EUR	PGC[129]
Tourette syndrome	1177	4955	13	0.74	EUR	TICG/TSAICG[130]
Other						
Chronic kidney disease	5807	56430	13	1.00	EUR	CKDGen[131]
Endometriosis	4604	9393	11	1.00	Mix	Nyholt[132]

Study acronyms: AC, the aneurysm consortium; **ALSGEN,** the International Consortium on Amyotrophic Lateral Sclerosis Genetics**; AMD Gene**, Age-related Macular Degeneration Gene Consortium; **BCAC**, Breast Cancer Association Consortium; **CARDIoGRAM**, Coronary ARtery DIsease Genome wide Replication and Meta-analysis; **CHARGE-HF**, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium – Heart Failure Working Group; **COPDGene**, The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease; **CKDGen**, Chronic Kidney Disease Genetics consortium; **CORECT**, ColoRectal Transdisciplinary Study; **DIAGRAM**, DIAbetes Genetics Replication And Meta-analysis; **EAGLE**, EArly Genetics & Lifecourse Epidemiology Eczema Consortium (excluding 23andMe); **ECAC**, Endometrial Cancer Association Consortium; **EPIC**, European Prospective Investigation into Cancer and Nutrition study; **GABRIEL**, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community; **GCAN**, Genetic Consortium for Anorexia Nervosa; **GECCO**, Genetics and Epidemiology of Colorectal Cancer Consortium; **IGAP**, International Genomics of Alzheimer's Project; **HPFS**, Health Professionals Follow-Up Study; **ILCCO**, International Lung Cancer Consortium; **IMSGC**, International Multiple Sclerosis Genetic Consortium; **IIBDGC**, International Inflammatory Bowel Disease Genetics Consortium; **KIDRISK**, Kidney cancer consortium; **MC**, the melanoma meta-analysis consortium; **METASTROKE/ISGC**, METASTROKE project of the International Stroke Genetics Consortium; **NBCS**, Nijmegen Bladder Cancer Study; **NHS**, Nurses' Health Study; **OCAC**, Ovarian Cancer Association Consortium; **PanScan**, Pancreatic Cancer Cohort Consortium; **PGC**, Psychiatric Genomics Consortium; **PRACTICAL**, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; **SLAGEN**, Italian Consortium for the Genetics of Ayotrophic Lateral Sclerosis; **T1DBase**, type 1 diabetes database; **TICG** (Tourette International Collaborative-Genetics); **TSAICG** (Tourette Syndrome Association International Consortium for Genetics);. **Abbreviations**: **ALS**, amyotrophic lateral sclerosis; **AMD**, age-related macular degeneration; **COPD**, chronic obstructive pulmonary disease; **EUR**, European; **EA**, East Asian; **LMP**, low malignant potential; **No.**, number; **Pop**., population; **SCC**, squamous cell carcinoma; **SNP**, single nucleotide polymorphism; **-ve**, negative; **+ve**, positive; †plus previously unpublished data.

Figure 1. The association between genetically increased telomere length and odds of primary non-communicable diseases

Legend to Figure 1

*P value for association between genetically increased telomere length and disease from maximum likelihood; the effect estimate for heart failure is a hazard ratio (all others are odds ratios); P_{het}, P-value for heterogeneity amongst SNPs within the instrument; COPD, chronic obstructive pulmonary disease; SNP, single nucleotide polymorphism; CI, confidence interval; LMP, low malignancy potential; ER, estrogen receptor; -VE, negative; +VE, positive.

Figure 2. The association between genetically increased telomere length and odds of cancer as a function of selected characteristics

Legend to Figure 2

The plotted data show how the strength of the relationship between genetically increased telomere length and cancer varies by the selected characteristic. The R^2 statistic indicates how much of the variation between cancers can be explained by the selected characteristic. P-values are from meta-regression models. Circle sizes are proportional to the inverse of the variance of the log odds ratio. The hashed line indicates the null of no association between telomere length and cancer (i.e. an odds ratio of 1). Data for percentage survival 5 years after diagnosis, cancer incidence and median age-at-diagnosis was downloaded from the Surveillance, Epidemiology, and End Results Program.[33] Data for average lifetime number of stem cell divisions was downloaded from Tomasetti and Vogelstein.[34] Not all cancers had information available for the selected characteristics (hence the number of cancers varies across the subplots). Information was available for 9 cancers for tissue-specific rates of stem cell division, 13 cancers for percentage surviving 5 years post-diagnosis, 17 cancers for cancer incidence and 13 cancers for median age-at-diagnosis. SD, standard deviation; OR, Odds ratio.

Figure 3. Comparison of genetic and prospective observational studies[†] of the association between telomere length and disease

Legend to Figure 3

*from fixed-effects meta-analysis of independent observational studies described in Table S3; [†]search strategy and characteristics for observational studies are described in Tables S3 and S4; ‡CCHS and CGPS; +PLCO, ATBC & SWHS (acronyms explained in Table S3); CI, confidence interval

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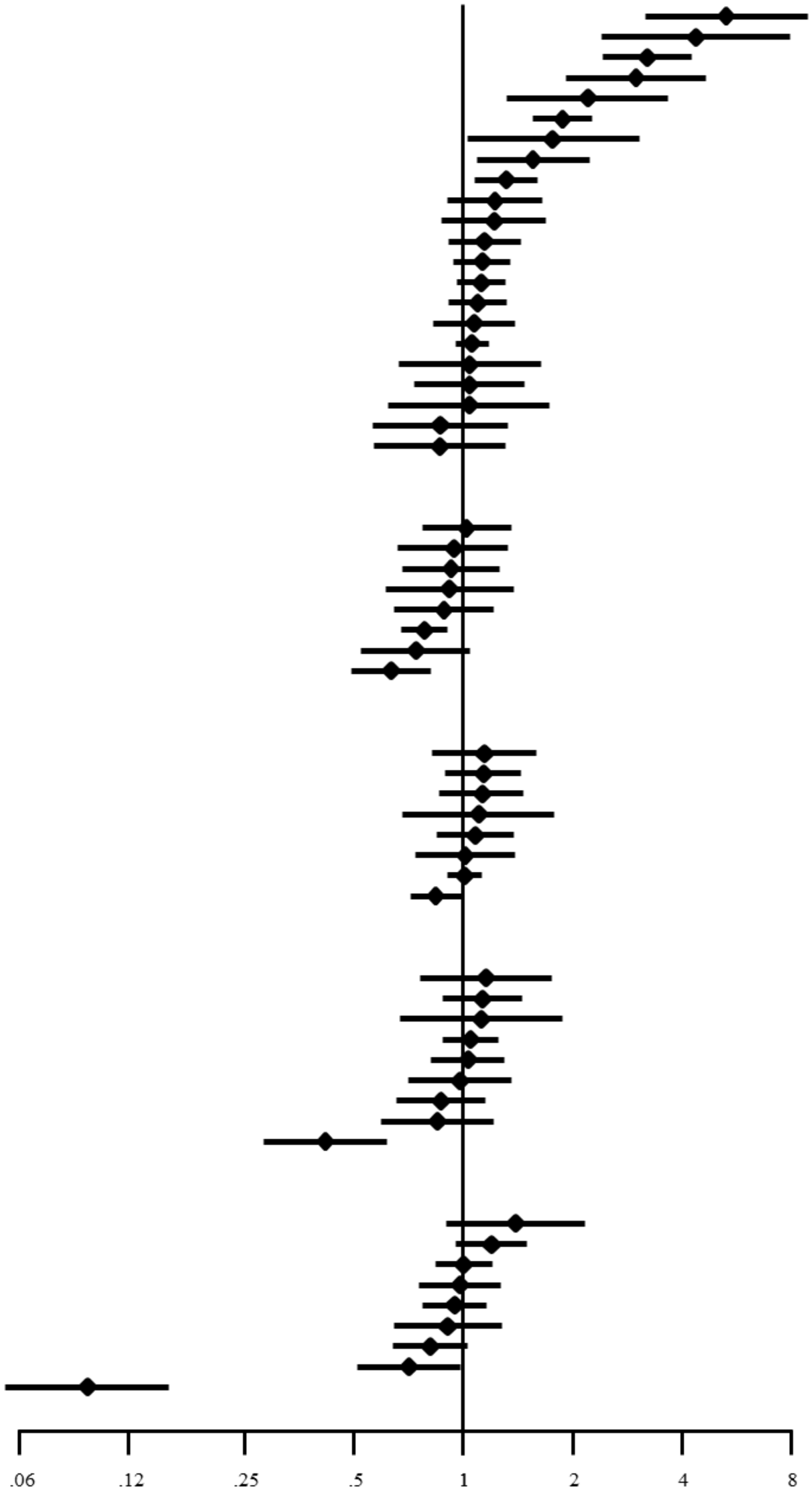
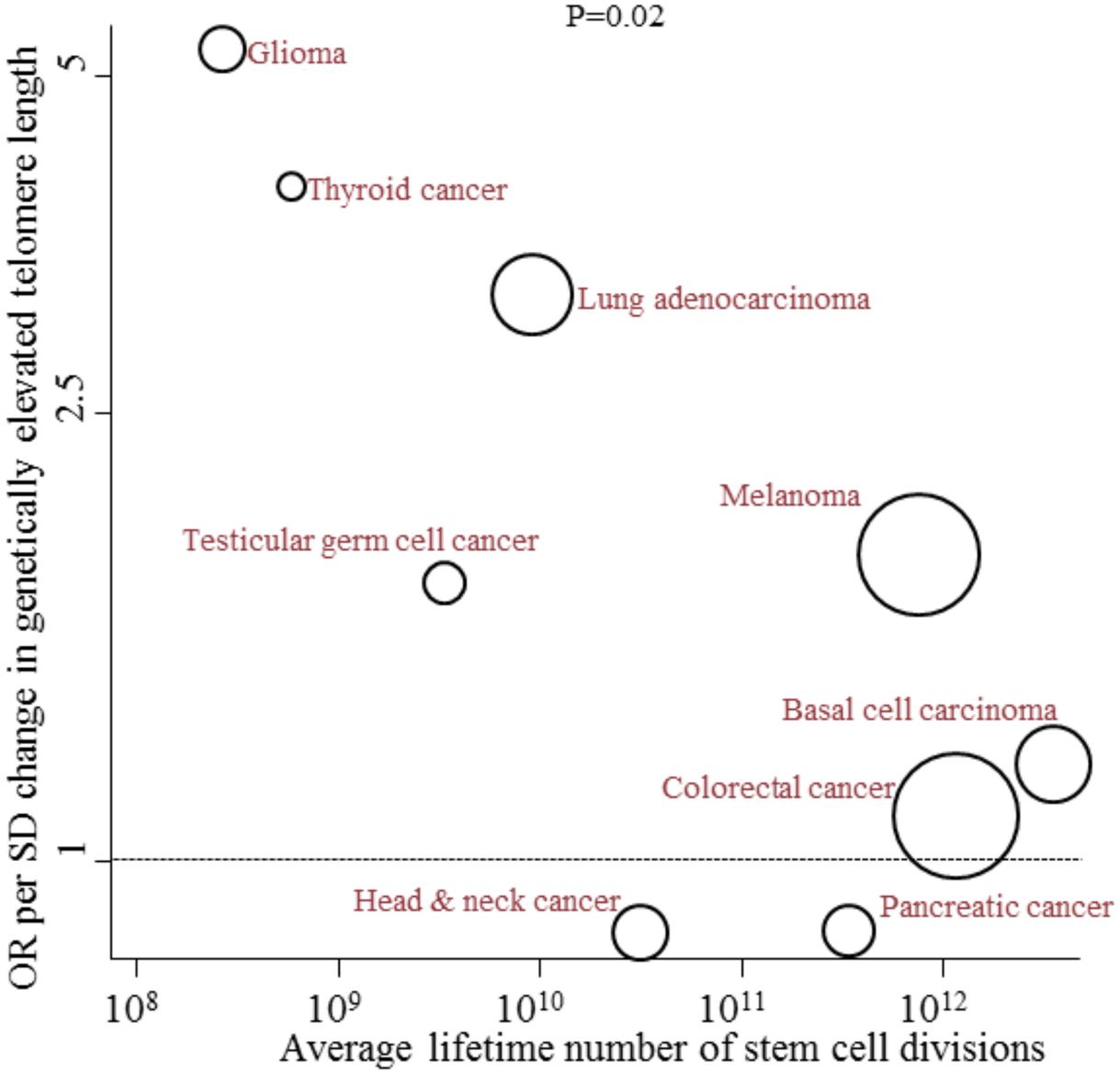
	Tumor/disease subtype	No. of cases	No. of SNPs	P*	P_{het}
Cancer					
Glioma	-	1130	12	$2.45x10^{-10}$	.0135
Ovarian cancer	Serous LMP	972	13	$1.62x10^{-6}$	.082
Lung cancer	Adenocarcinoma	3442	13	$6.66x10^{-16}$	.0001
Neuroblastoma	-	2101	12	$1.11x10^{-6}$	.3799
Bladder cancer	-	1601	10	.0026	.2541
Skin cancer	Melanoma	12814	13	$5.79x10^{-11}$	.086
Testicular germ cell cancer	-	985	11	.0423	.3002
Kidney cancer	-	2461	12	.0164	.251
Endometrial cancer	-	6607	12	.0091	.1436
Skin cancer	Basal cell carcinoma	3361	13	.203	.0398
Ovarian cancer	Endometriod	2154	13	.2499	.3319
Breast cancer	ER-ve	7465	13	.2542	<0.0001
Ovarian cancer	Serous invasive	9608	13	.2088	.0407
Prostate cancer	-	22297	11	.1533	<0.0001
Colorectal cancer	-	14537	9	.3436	.0156
Lung cancer	Squamous cell carcinoma	3275	13	.6212	.9042
Breast cancer	ER+	27074	13	.2912	.0228
Ovarian cancer	Clear cell	1016	13	.8676	.3226
Ovarian cancer	Mucinous	1643	13	.8396	.3147
Esophageal cancer	Squamous cell carcinoma	1942	8	.9055	.4513
Pancreatic cancer	Adenocarcinoma	5105	12	.5009	.0016
Head & neck cancer	-	2082	12	.4767	.0763
Cardiovascular diseases					
Heart failure	-	2526	13	.8931	.5348
Ischemic stroke	Small vessel disease	1894	13	.7141	.2358
Sudden cardiac arrest	-	3954	13	.62	.5400
Intracerebral stroke	-	5503	12	.6719	.0002
Ischemic stroke	Cardioembolic	2365	13	.4464	.0374
Coronary heart disease	-	22233	13	.0009	.2441
Ischemic stroke	Large vessel disease	2167	13	.0801	.1578
Abdominal aortic aneurysm	-	4972	13	.0003	.0617
Neurological / psychiatric diseases					
Anorexia Nervosa	-	2907	9	.4406	.1797
Bipolar disorder	-	7481	9	.315	.1427
Amyotrophic lateral sclerosis	-	6100	12	.4049	.6331
Tourette syndrome	-	1177	13	.6936	.4978
Major depressive disorder	-	9240	8	.5646	.254
Autism	-	4949	7	.9514	.8232
Schizophrenia	-	9379	12	.9245	.0053
Alzheimer's disease	-	17008	12	.0296	.1451
Autoimmune/inflammatory diseases					
Alopecia areata	-	2332	7	.4994	.9505
Inflammatory bowel disease	Crohn's disease	5956	11	.3586	.0585
Periodontitis	-	888	13	.6702	.0066
Atopic dermatitis	-	10788	13	.6094	.1194
Inflammatory bowel disease	Ulcerative colitis	6968	12	.8303	.0984
Multiple sclerosis	-	14498	3	.8885	.1455
Rheumatoid arthritis	-	5538	11	.3184	.1828
Juvenile idiopathic arthritis	-	1866	11	.3669	.922
Celiac disease	-	4533	3	$1.00x10^{-5}$	.0028
Other diseases					
Retinopathy	-	1126	12	.1453	.3831
Age-related macular degeneration		7473	13	.1206	.209
Type 2 diabetes	-	10415	11	.9837	.6811
Endometriosis	-	4604	11	.8606	.0576
Chronic kidney disease	-	5807	13	.5859	.6972
COPD	-	2812	12	.5598	.3807
Asthma	-	13034	4	.0779	.3213
Type 1 diabetes	-	7514	6	.0378	.0586
Interstitial lung disease	-	1616	9	$2.02x10^{-19}$	.0014



Average lifetime number of stem cell divisions

Adjusted R^2=52.63%

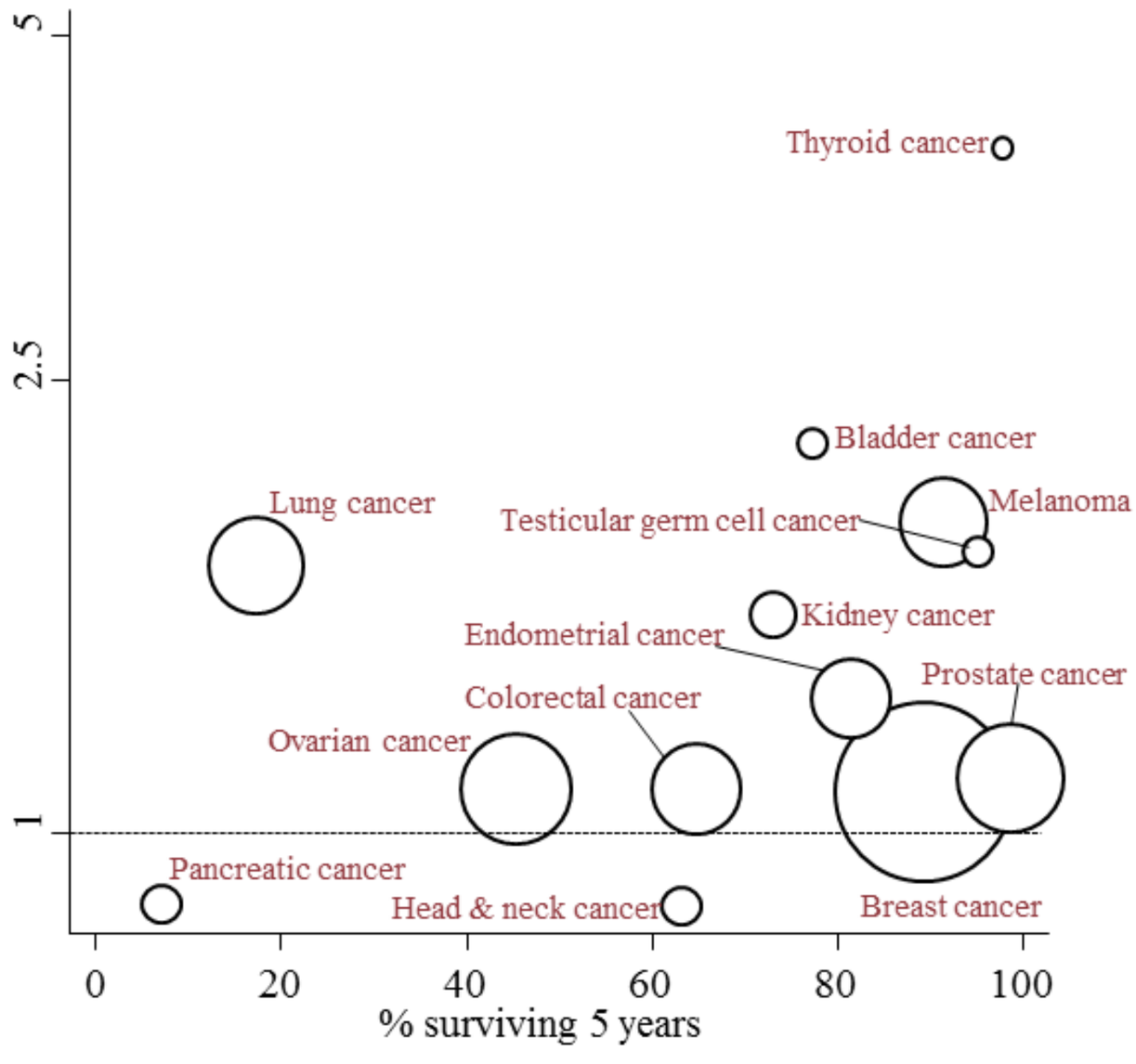
P=0.02



% surviving 5 years

Adjusted R^2=-19.49%

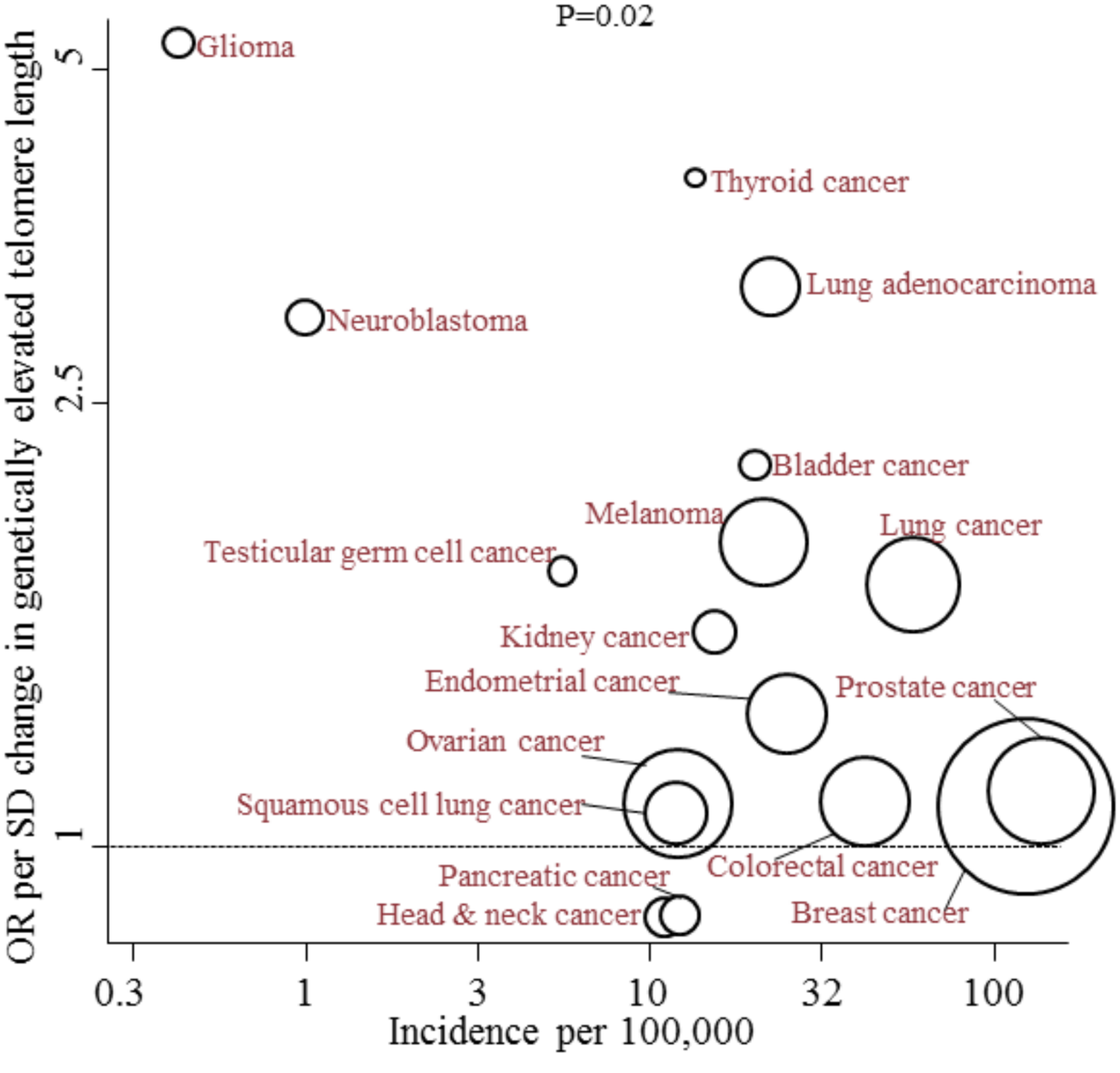
P=0.37



Cancer incidence

Adjusted R^2=32.12%

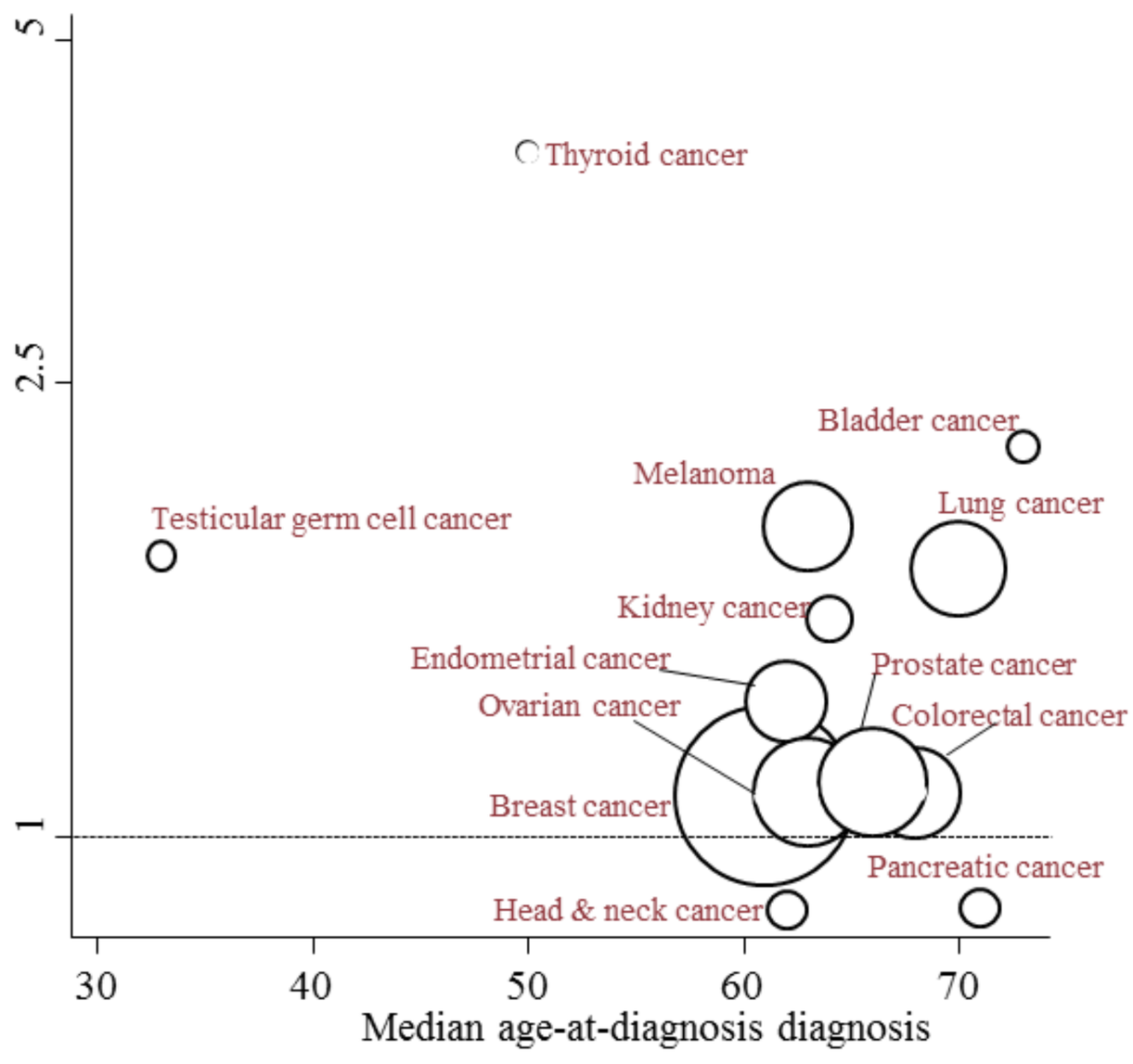
P=0.02



Median age-at-diagnosis diagnosis

Adjusted R^2=-8.86%

P=0.41



	No. of cases	Odds ratio (95% CI) per standard deviation increase in telomere length
Cancer		
Breast cancer		
Genetic study	48155	1.08 (0.99, 1.19)
Observational study*	1716	1.02 (0.99, 1.05)
Prostate cancer		
Genetic study	22297	1.12 (0.96, 1.30)
Observational study*	1340	1.07 (1.01, 1.14)
Ovarian cancer		
Genetic study	15397	1.09 (0.94, 1.27)
Observational study	96	1.13 (0.98, 1.32)
Colorectal cancer		
Genetic study	14537	1.09 (0.91, 1.31)
Observational study*	1447	1.04 (0.97, 1.11)
Lung cancer		
Genetic study	11348	1.71 (1.44, 2.04)
Observational study‡	522	0.94 (0.87, 1.02)
Observational study+	847	1.28 (1.12, 1.46)
Endometrial cancer		
Genetic study	6608	1.31 (1.07, 1.61)
Observational study*	382	1.06 (0.95, 1.19)
Pancreatic cancer		
Genetic study	5105	0.86 (0.56, 1.32)
Observational study*	648	1.05 (0.95, 1.17)
Lung adenocarcinoma		
Genetic study	3442	3.19 (2.40, 4.22)
Observational study	288	1.44 (1.14, 1.82)
Skin basal cell carcinoma		
Genetic study	3361	1.22 (0.90, 1.65)
Observational study	363	0.96 (0.85, 1.09)
Lung squamous cell carcinoma		
Genetic study	3275	1.07 (0.82, 1.39)
Observational study	163	1.05 (0.78, 1.42)
Kidney cancer		
Genetic study	2461	1.55 (1.08, 2.23)
Observational study*	268	0.94 (0.81, 1.10)
Head & neck cancer		
Genetic study	2082	0.86 (0.57, 1.30)
Observational study	76	0.89 (0.72, 1.09)
Melanoma		
Genetic study	12814	1.88 (1.54, 2.28)
Observational study*	734	1.17 (1.06, 1.29)
Bladder cancer		
Genetic study	1601	2.19 (1.32, 3.66)
Observational study	184	1.28 (1.02, 1.61)
Testicular cancer		
Genetic study	986	1.76 (1.02, 3.04)
Observational study	10	0.94 (0.56, 1.55)
Glioma		
Genetic study	1130	5.27 (3.15, 8.81)
Observational study	101	0.90 (0.68, 1.18)
Non-neoplastic diseases		
Coronary heart disease		
Genetic study	22233	0.78 (0.67, 0.90)
Observational study	2272	0.86 (0.78, 0.94)
Ischemic stroke		
Genetic study	12389	0.85 (0.73, 1.00)
Observational study	824	0.94 (0.82, 1.08)
Type 2 diabetes		
Genetic study	10415	1.00 (0.84, 1.20)
Observational study	2011	0.90 (0.83, 0.97)